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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,341	03/20/2001	Kathy L. Miller	P1780R1	1230

7590 03/04/2005

Attn: Wendy M. Lee
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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/813,341	MILLER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,11-15,21,25,26,33-37,41,42,57-66,68,69 and 74-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-15,21,25,26,33-37,41,42,57-66,68,69 and 74-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 02/23/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's submission filed on 09/22/2004, and 12/09/2004 is acknowledged. Claims 33, 61, and 66 are amended. Claims 1, 2, 4-9, 11-15, 21, 25, 26, 33-37, 41, 42, 57-66, 68, 69, 74-80 are pending, and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 102, Maintained

Claims 1, 2, 4, 8, 9, 12-15, remain rejected under 35 U.S.C. 102(b) as being anticipate by Alderson et al (1994, International Immunology, vol. 6, pages 1799-1806).

Claims 1, 2, 4, 8, 9, 12-15 are interpreted as drawn more than three antigen binding sites with specified structural and functional characteristic i.e. comprising a polypeptide chain comprises two or more variable domains (claim 4), comprises at least two light chain variable domain polypeptides (claims 8), further comprises a CL domain (claim 9), internalizes faster than a bivalent antibody (claim 12), an agonist antibody (claim 13), induces apoptosis (claim 14), monospecific (claim 15).

Applicant argues that Alderson et al., discloses an anti-Fas IgM antibody. The authors do not disclose an isolated antibody comprising an Fc region wherein three or more antigen binding sites are amino terminal to the Fc region. A native IgM antibody contains an Fc region and multiple binding regions, but there is only one or two antigen binding regions(s) amino-terminal to an Fc region, not three or more as Applicant claim or the four antigen binding sites of the claimed elected species. These arguments have been fully considered but found unpersuasive.

The rejected claims still read on IgM anti-huFas mAb at page 1800, left column, line 2 of Alderson. Contrary to applicant's argument that there is only one or two antigen binding regions amino-terminal to an Fc region, there are 10 binding regions in IgM anti-huFas mAb. Each and every one of those 10 binding regions are located amino-terminal to the Fc. None of those 10 binding regions are carboxy-terminal to the Fc region. The vague claim limitations as to the claimed antibody or protein structures in the base claim 1 in light of the prosecution history i.e. the inventor's 131 declaration antedating the art of record, Santos et al and Alt et al, wherein the declaration states that two Fabs are located amino-terminal to an Fc, which indicate that more than three binding sites are result of two different antibody chain joined by disulfide bonding between the two antibody chains with the construct shown at page 9 of the note book in inventor's 131 declaration. Note instant specification at Fig. 2E IgM for a pictorial diagram, which shows that IgM with more than three binding sites comprising at least two light chain variable domain polypeptides, further comprises a CL domain, a dimerization domain could be a hinge region, an Fc region, a CH3 domain, or CH4 domain. Alderson et al teach IgM anti-huFas mAb induces apoptosis (note abstract, second paragraph of Introduction at page 1799), binds only one antigen i.e. Fas that belongs to TNF receptor family (note the instant specification at page 8, line 14-32 says that Fas belongs to TNF receptor family). The IgM anti-huFas mAb appears to be an agonist antibody because Fas and the antibody both sends same signal i.e. sending apoptosis signal. As for claims 12, applicant does not argue. As stated before, the Office does not have the facilities and resources to provide the factual evidence needed

in order to establish that the composition of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed composition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed composition is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103, Maintained

Even if applicant could overcome 102 (b) rejection above, claims 1, 2, 4-9, 12-15, 57-66, 68, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9).

The claims are interpreted as drawn to an engineered antibody with three or more antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species), wherein said polypeptide has a Fc region at its amino terminus, wherein said antibody has the recited functions i.e. agonist, internalized faster, induces apoptosis. Note above under 102(b) rejection above for further detail of the instant claims.

Applicant argues that neither Zapata et al. nor Shu et al. contemplate, much less disclose, an isolated antibody as claimed by Applicants having four antigen (or even three or more) binding sites. The combination of Zapata et al. and Shu et al., cannot add what is not found in either reference: namely, the presence of four (or three or more) antigen binding regions amino terminal to an Fc or a dimerization region. Such an

antibody would not have been obvious to one of ordinary skill in the art reading the cited references because such a teaching was not available prior to Applicants' disclosure. There is no teaching or motivation in the literature to generate an antibody having four (or three or more) antigen binding sites amino-terminal to an Fc or a dimerization region. Applicants respectfully submit that it is only through impermissible use of hindsight available only through reference to Applicants' patent disclosure that the Examiner has crafted the rejection.

Applicant's arguments have been fully considered but found unpersuasive. Regarding applicant's argument that the references do not teach presence of three or more binding sites, the combination of Zapata et al., and Shu et al., do teach each and every element of the claimed invention. As stated in the previous Office action, Zapata et al., teach an engineered antibody with a polypeptide structure of VH-CH1-VH-CH1 at page 1058 (see Fig. 1) with 2 of VL-CL attached. This structure has possibility of becoming four antigen binding sites if two polypeptides are linked by Fc from each of the polypeptides. As for motivation to arrive at three or more binding sites, Zapata et al., teach the engineered antibody $F(ab')_2$ (with more antigen binding sites than Fab) kills cancer cells better (higher antiproliferate activity than Fab), has longer serum half-life than Fab. Note abstract, Figs. 1-5, and Table I and II. Zapata et al., thus suggest that more binding sites of an engineered antibody might result in a more desirable antibody i.e. higher avidity and prolonged serum half-life, thus less frequent painful injections in clinical use.

Although Zapata et al., do not specifically teach an isolated antibody comprising an Fc region and antigen binding sites amino-terminal to the Fc region, Shu et al., teach an isolated antibody comprising an Fc region and antigen binding sites amino-terminal to the Fc region (note Fig. 2 for picture). Shu et la., teach that human Fc region has an effector functions such Fc receptor binding necessary for certain antibody activity (note page 7995 left column, especially the first paragraph of Shu et al) and also teach way to make multivalent engineered antibody is to add human γ1 Fc region through hinge region such that the polypeptide has region to form dimeric structure (note Fig. 2), and further teach antibody comprising a polypeptide comprising human γ1 Fc region is advantageous because it is immunoglobulins-like and make ex vivo transfection of cells for the delivery of the tumoricidal antibody to the tumor site for gene therapy.

Regarding applicant's argument that the instantly claimed antibody would not have been obvious to one of ordinary skill in the art reading the cited references because such a teaching was not available prior to Applicants' disclosure, the skill in the antibody engineering art had been very high before the effective filing date of the instant application as taught by Zapata et al, and Shu et al. It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make an antibody comprising a polypeptide structure of VH-CH1-VH-CH1 (as taught by Zapata et al.,), which gives two binding sites with a polypeptide, linked to Fc since Shu et al., teach that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized, resulting in four binding sites.

One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product with reasonable expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life, thereby reducing painful injections and saving money by using less of the product in clinical use.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claims 1, 2, 4-9, 12-15, 21, 25, 26, 33-37, 41, 42, 57-66, 68 and 74-78 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9, secondary reference), and further in view of WO 98/41629 (IDS, 24 September 1998).

As a formal matter, it is noted that claims 21, 25, 26, 33-37, 41, 42 were also included in the rejection in the Office action mailed on 02/20/2004 (note last three lines of page 8 of the Office action).

The claims are interpreted as drawn to an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) with the recited functions i.e. agonist, internalized faster, induces apoptosis, wherein said antibody binds to DR5.

Applicant argues that the non-obviousness of Applicants' invention in view of rejection over the Zapata and Shu references is stated above. W098/41629 discloses DR5, the antigen species elected by Applicants. The addition of the particular antigen to which an antibody of Applicants' invention may bind fails to cure the deficiency of the Zapata and Shu references discussed above. The deficiency is the absence of any suggestion or teaching in Zapata or Shu of an antibody having four (or three or more) antigen binding sites amino-terminal of an Fc region or a dimerization region. The teaching of the particular antigen to which a bivalent antibody (of the Zapata and/or Shu references) binds does not yield an antibody having four (or three or more) antigen binding sites to DR5 or to any antigen. These arguments have been fully considered but found unpersuasive.

The obviousness of an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) with the recited functions i.e. agonist, internalized faster, induces apoptosis is explained in the 103 (a) above. In this section, only the tertiary reference, WO 98/41629 would be

explained. WO 98/41629 teaches antibody to DR5 (see page 36 lines 25 to page 37 lines 5, claims 21, 25, 26) and also teaches agonist antibody useful for treating cancer and other proliferative diseases at page 37 line 5, page 38 lines 31-35.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make an DR-5 binding antibody (useful to treat cancer, cancer treating antibody could generate a lot of revenue) comprising a polypeptide structure of VH-CH1-VH-CH1 (as taught by the primary reference which gives two binding sites) linked to Fc since the secondary reference teaches that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized. One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product with reasonable expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life DR-5 antibody capable of killing cancer cells, thereby reducing painful injections and saving money by using less of the product in clinical use.

Claims 66, 75, and 80 remain rejected under **35 U.S.C. 103(a)** as being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages

7995-9, secondary reference), and in further in view of Paprocka et al (1992, Arch Immunol. Ther Exp, vol. 40, pages 223-7, abstract only).

As a formal matter, it is noted that claims 66, 75, and 80, not all of the claims applicant lists at page 8 of the Remark section filed on 08/17/04 are rejected in the Office action mailed on 02/20/2004 (note page 10 of the Office action).

The rejected claims are interpreted as drawn to an engineered antibody with four antigen binding sites comprising a polypeptide structure of VH-CH1-VH-CH1 (the elected species) linked to a cytotoxic agent.

Applicant argues that the non-obviousness of Applicants' invention in view of rejection over the Zapata and Shu references is stated above. In this rejection, the Examiner further interprets the claims to be drawn to an antibody linked to a cytotoxic agent. Paprocka et al. disclose linking ricin (a cytotoxic agent) coupled to a monoclonal antibody. Such a teaching fails to cure the deficiency of the Zapata and Shu references are argued above. The absence of a teaching of four (or three or more) antigen binding sites amino- terminal to ah Fc region or a dimerization region of an antibody is the deficiency of the Zapata and Shu references alone or in combination. The teaching of a linked cytotoxic agent by Paprocka et al. does not cure this deficiency. These arguments have been fully considered but found unpersuasive.

The combination of Zapata and Shu references teaches each and every element of the claimed invention and so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. As stated before in the previous Office action, Paprocka et al., reference teaches that making and using an immunoconjuate linking an antibody to a cytotoxic agent such as ricin for cytotoxic effect is an art-known technique well before the effective filing date of the instant application.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make antibody (useful to treat cancer, cancer treating antibody could generate a lot of revenue) comprising a polypeptide structure of VH-CH1-VH-CH1 linked (as taught by the primary reference which gives two binding sites) linked to Fc since the secondary reference teaches that Fc has the effector benefit and also teach that the structure comprising γ1 Fc region through hinge region has a dimerization domain, which double the antigen binding sites once the polypeptide becomes dimerized. One having ordinary skill in the art at the time the claimed invention would be motivated to make the claimed product by linking to a cytotoxic agent (taught by tertiary reference) with reasonable expectation of success because by linking the structure taught by the primary reference and secondary references because the combined structure will result in antibody with more desirable properties i.e., one with the Fc effector function, higher avidity and/or increased half-life DR-5 antibody capable of killing cancer cells, thereby reducing painful injections and saving money by using less of the product in clinical use.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU
PATENT EXAMINER

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/2/05